ABSTRACT

Temozolomide (TMZ) is an oral alkylating agent used during concurrent and adjuvant chemotherapy for newly diagnosed glioblastoma multiforme. Temozolomide is generally well tolerated and improves survival; however, severe adverse events have occasionally been reported. Here, we report the case of a patient who developed aplastic anemia with related complications in the setting of concurrent TMZ treatment with radiotherapy. This case illustrates that aplastic anemia is a rare side effect of TMZ that can occur relatively early in the course of concurrent chemotherapy, and underscores the importance of clinician awareness of this potentially devastating side effect.

KEY WORDS

Glioblastoma multiforme, temozolomide, pancytopenia, aplastic anemia

1. INTRODUCTION

Temozolomide (TMZ) is an oral alkylating agent used during concurrent and adjuvant chemotherapy for newly diagnosed glioblastoma multiforme (GBM). Temozolomide is generally well tolerated and improves survival; however, severe adverse events have occasionally been reported. Here, we report the case of a patient who developed aplastic anemia with related complications in the setting of TMZ treatment concurrent with radiotherapy.

2. CASE DESCRIPTION

A 63-year-old woman presented to the emergency department with a 6-week history of progressive comprehension difficulties. Initial computed tomography imaging of her head revealed a heterogeneously enhancing mass in the left temporal region with surrounding edema. She was started on dexamethasone and achieved significant improvement in symptoms.

Because of the metastatic appearance of the lesion, a thorough search, which proved unremarkable, was performed for a primary malignancy. The patient subsequently underwent craniotomy and tumour excision for diagnostic purposes. The biopsy showed evidence of anaplastic astrocytoma, World Health Organization grade IV, consistent with GBM.

This woman’s past medical history was otherwise remarkable for hypertension, hypothyroidism, and multiple bladder repair surgeries with recurrent urinary tract infections (UTIs). Her medications included levothyroxine, lisinopril, amlodipine, ranitidine, and omeprazole. Her initial hematology work-up before commencing treatment was within normal range: hemoglobin 133 g/L, white blood cells (WBCs) 12.7×10⁹/L, neutrophils 11.2×10⁹/L, platelets 253×10⁹/L (Table 1).

The patient began treatment with radiotherapy and concurrent TMZ. Clinically, she tolerated both the radiation therapy and TMZ quite well, with fatigue as the only evident side effect. However, after 15 of 22 fractions of radiation therapy, and 18 of 42 days of TMZ, her lab work showed a significant drop in all blood-cell lines (hemoglobin 88 g/L, WBCs 0.3×10⁹/L, neutrophils 0.1×10⁹/L, platelets 30×10⁹/L; Table 1). She complained of urinary frequency, urgency, and dysuria, but was afebrile and showed no other signs of infection. She was instructed to discontinue TMZ and was prescribed antibiotics to treat the UTI.

Repeat lab work 3 days later showed persistent pancytopenia (hemoglobin 66 g/L, WBCs 0.1×10⁹/L, platelets 89×10⁹/L; Table 1). The patient was then transfused with 10 units of platelets and 2 units of packed red blood cells (PRBCs). Her temperature spiked, and she became progressively fatigued and developed a headache. She also complained of symptoms of severe dysphagia with evident mucositis and thrush. She was started empirically on a 10-day course of ciprofloxacin and was given oral mouthwash for the thrush. She completed her course of radiotherapy as planned.

The woman was hospitalized 2 days later with persistent pancytopenia (hemoglobin 92 g/L, WBCs 0.2×10⁹/L with no neutrophils, platelets 30×10⁹/L;
Table 1, an occipital headache, and persistent fever. She was started on broad-spectrum antibiotics—meropenem, fluconazole, and acyclovir—to treat the febrile neutropenia, concurrent thrush, and possible herpes simplex virus stomatitis (which was not confirmed on viral biopsy). Blood cultures eventually grew *Fusobacterium.*

A bone marrow aspirate revealed nearly acellular marrow with rare normoblasts and neutrophils. There were no evident megakaryocytes, clusters of blast cells, lymphoid aggregates, granulomata, or metastatic cells. Those findings, in conjunction with the clinical picture, were suggestive of a hypoplastic or aplastic cause for this patient’s pancytopenia.

The woman required a prolonged 4-week hospitalization for the persistent pancytopenia. She was started on filgrastim and erythropoietin in the week before her discharge, and her WBCs had recovered somewhat to 1.4×10⁹/L with neutrophils at 0.6×10⁹/L after 1 week (Table 1).

The patient was readmitted 2 days later with headache, confusion, and expressive aphasia. Computed tomography imaging of the head at this time showed evidence of GBM recurrence in the left temporal lobe. On filgrastim, her WBCs increased substantially to 4.1×10⁹/L. She continued to require transfusions of platelet and PRBCs. Given that she was unable to tolerate the TMZ, her prognosis at that point was deemed to be only a few months. She was discharged home with palliative services.

### 3. DISCUSSION

Aplastic anemia occurs because of injury to the pluripotent stem cell, which results in decreased or absent hematopoietic precursor cells in bone marrow. Aplastic anemia can be congenital, acquired, or idiopathic. The acquired causes of aplastic anemia are diverse and include drugs, chemicals, infections, and radiation. Most cases of acquired aplastic anemia are ultimately deemed idiopathic.

The diagnosis of aplastic anemia is established by bone marrow aspirate. Features consistent with aplastic anemia include profoundly hypocellular marrow with normal morphology of the residual hematopoietic stem cells, an absence of malignant infiltrates, and an absence of megaloblastic hematopoiesis.

The known side effects of TMZ are generally mild to moderate. The most serious side effect of TMZ is myelotoxicity, which is dose-dependent and usually reversible. In a trial conducted by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada, Stupp and colleagues documented the development of grades III and IV hematotoxicity in 7% of patients receiving concurrent TMZ and in 14% of patients receiving adjuvant TMZ.

In the existing literature, 4 previous cases of aplastic anemia in the context of TMZ administration have been reported (Table 2). Two of those cases occurred later in the course of TMZ treatment, after completion of concurrent TMZ chemotherapy. In one case, aplastic anemia occurred during concurrent TMZ administration, but the contributory effects of trimethoprim sulfamethoxazole could not be excluded. Our patient developed aplastic anemia very early in the course of concurrent TMZ administration, in the absence of other likely contributing medications—a situation that has been previously described in only 1 recent case.

Given the many different causes of acquired aplastic anemia, it is difficult to definitively establish the cause of our patient’s aplastic anemia. Of this woman’s other medications, the only potential offending agent was ranitidine; however, the patient had already been on that medication, with no evidence of hematologic toxicity, before the TMZ was administered. In light of the temporal sequence of events, and in the absence of any other prescription medications known to cause this syndrome, the most likely cause of this patient’s aplastic anemia was TMZ.

### 4. CONCLUSIONS

This case shows that aplastic anemia is a rare side effect of TMZ that can occur relatively early in the course of concurrent chemotherapy, and it underscores the importance of clinician awareness of this potentially devastating side effect.
APLASTIC ANEMIA AND TMZ

ACKNOWLEDGMENTS

Dr. James R. Perry is the Crolla Family Chair in Neuro-Oncology at the University of Toronto.

CONFLICT OF INTEREST DISCLOSURES

The authors all declare that no financial conflicts of interest exist.

REFERENCES


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### Table II

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient</th>
<th>Time course of the development of aplastic anemia</th>
<th>Potential contributing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doyle et al., 2005</td>
<td>NA</td>
<td>During concurrent phase of RT/TMZ administration</td>
<td>Trimethoprim–sulfamethoxazole</td>
</tr>
<tr>
<td>Villano et al., 2006</td>
<td>45 Male</td>
<td>During cycle 4 of adjuvant TMZ administration</td>
<td>None</td>
</tr>
<tr>
<td>Jalali et al., 2007</td>
<td>30 Female</td>
<td>After completing course of concurrent TMZ</td>
<td>Trimethoprim–sulfamethoxazole, phenytoin</td>
</tr>
<tr>
<td>Morris et al., 2009</td>
<td>16 Female</td>
<td>During concurrent phase (day 24) of RT/TMZ administration</td>
<td>None</td>
</tr>
<tr>
<td>Present case</td>
<td>63 Female</td>
<td>During concurrent phase (day 18) of RT/TMZ administration</td>
<td>Ranitidine (unlikely contributor)</td>
</tr>
</tbody>
</table>

*RT = radiotherapy.*